NEUROFIBROMATOSIS TYPE 1 (NF1) GENE THERAPY INITIATIVE

REQUEST FOR APPLICATIONS

The Children’s Tumor Foundation (CTF) neurofibromatosis type 1 (NF1) Gene Therapy Initiative is requesting applications for projects exploring gene therapy approaches to treating NF1 plexiform neurofibromas (pNF) and/or malignant peripheral nerve sheath tumors (MPNST).

BACKGROUND

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic syndrome affecting 1 in 3000 people worldwide. The hallmark of NF1 is the development of multiple peripheral nerve sheath tumors, including cutaneous (cNF) and plexiform neurofibromas (pNF), which, although histologically benign, cause significant morbidity. Several studies have suggested that these benign Schwann cell tumors may have subtypes based on gene expression patterns. Other characteristics include skin findings such as café-au-lait macules, axillary or inguinal freckling, additional tumors such as optic pathway gliomas, gastrointestinal stromal tumors, pheochromocytomas and gangliogliomas as well as bone and vascular anomalies, and a high incidence of cognitive difficulties. pNF in about 10-15% of NF1 patients can develop into MPNSTs, which carry a poor prognosis. NF1 patients are also predisposed to other malignancies, including breast cancer. The manifestations and clinical severity of NF1 are highly variable, with significant differences that may even occur within the same family.

Mutations in the NF1 gene cause this syndrome, and 50% of cases are due to new mutations without any family history. The NF1 protein product, neurofibromin, is a large protein whose middle portion negatively regulates Ras signal transduction. Lack of normal neurofibromin function due to NF1 mutation allows constitutive activation of the Ras effector pathways, leading to altered downstream functions such as cell proliferation. Other functions of neurofibromin are less-characterized, such as regulation of cAMP. The NF1 germline mutational spectrum is exceptionally large, with over 5000 mutations comprising splice site, nonsense, missense, and frameshift mutations, as well as insertions, deletions, and translocations reported. Most appear to result in decreased neurofibromin activity, although recent work suggests that some may function via a dominant negative mechanism, affecting neurofibromin
homodimers. No single mutation has a frequency over ~5%. The involvement of epigenetics in tumor initiation and progression is unclear in pNF, but PRC2 complex function is often disrupted in MPNSTs. The variable expressivity of NF1 has precluded establishing clinically relevant genotype-phenotype correlations with the exception of a small selection of mutations. Most NF1 features involve clonal expansion of a cell that suffered somatic mutation of the other NF1 allele (two-hit phenomenon); the somatic mutation spectrum is equally broad. For example, neurofibromas arise from Schwann cells containing an NF1 mutation on both alleles, which ultimately lead to enhanced cell proliferation and survival. Thus, the impact of many NF1 mutations is not well-characterized at the protein level, and may be quite diverse, which may explain some NF1 clinical variability including tumor response. NF1 is also frequently somatically mutated in non-syndromic cancers such as sporadic melanoma, glioblastoma, AML, lung, ovarian, breast, pancreatic, and prostate cancers.

Until recently, there were no effective therapies for NF1 tumors other than surgical debulking, which can be extremely complicated if the tumor is intricately involved with nerve tissue, vasculature, or a vital organ. Two years ago, a MEK inhibitor was approved for inoperable plexiform neurofibromas in children, having been shown to variably shrink the tumors. However, about 30% of patients do not respond, and others can’t tolerate the medication. Surgery is rarely performed for NF1 optic pathway gliomas because of their location and resulting blindness, with the only non-surgical option being chemotherapy. Given NF1’s diversity of clinical expression/progression and complicated underlying biology, additional therapeutic approaches such as gene therapy need to be considered.

OBJECTIVE AND SCOPE

The objective of this Request for Applications (RFA) is to support studies to investigate the feasibility of gene therapy strategies to treat NF1 plexiform neurofibromas and/or MPNSTs. Investigators should describe and provide rationale for the target(s), therapeutic molecules, method(s) of therapy delivery, outcome measures to evaluate success and off-target effects, feasibility, and applicability among NF1 patients. All approaches will be considered. Innovation using newest approaches to optimize success while minimizing risk will be viewed particularly favorably. Investigators should outline how their approach, if successful, would lead to clinical application. Investigative groups should not only contain expertise in the strategy and tumor therapeutics, but familiarity with NF1. CTF will be happy to guide teams to NF1 expert consultants/collaborators as needed.

CTF intends to allot up to $1.5M to fund approximately three applications. Funding of applications is contingent upon the number of applications received, the quality and merit of the applications as evaluated by our review panel, and the requirements of this RFA.
APPLICANT ELIGIBILITY

- Principal Investigator should have an MD, PhD, or equivalent, with an established record of independent research, and must have full access to, or identified collaborators with, all required resources.

- Applications are welcomed from both the academic and private sectors. Partnerships between the two are actively encouraged, pending patent policy agreement (see below). If applicants are partnering with a contract research organization (CRO), a quote for service fees should be included in the application. However, CTF will not be responsible for any additional expenses incurred by the CRO.

- More than one investigator from an institution can apply provided that the research hypothesis and team composition are distinct. Multiple applications from the same PI will not be considered.

- There are no citizenship requirements for this award. Qualified individuals from within and outside the United States are eligible to apply.

- CTF requires all applicants to acquire a personal ORCID ID (https://orcid.org/) and to elect CTF as a trusted partner on ORCID. Once an applicant has granted permission, CTF as the trusted organization will be able to see information that they have set as visible to trusted parties in addition to the information set as visible to everyone. Please visit this ORCID page to learn more about visibility settings and trusted organizations. Since ProposalCentral, the grants management platform used by CTF, has developed an extended integration with ORCID to allow seamless data transfer, applicants are strongly encouraged to keep their ORCID ID record up to date especially in the Education, Funding and Works (publications) sections.

DIVERSITY, EQUITY, AND INCLUSION (DEI) STATEMENT

CTF is committed to fostering, cultivating, and preserving a culture of diversity, equity and inclusion. We embrace and encourage our applicants differences in backgrounds, experiences, race, color, religious creed, sex, national origin, ancestry, citizenship status, family or marital status, physical, mental and/or intellectual abilities, age, military or veteran status, registered domestic partner or civil union status, gender and gender identity, sexual orientation, political affiliation, and socioeconomic status.
COMMITMENT TO OPEN SCIENCE AND DATA SHARING

CTF values the open sharing of research outputs and since 2018 has funded the NF Data Portal, a public data repository that stores and shares data generated by multiple collaborative research programs focused on neurofibromatosis (NF) diseases (neurofibromatosis type 1, type 2, and schwannomatosis).

By applying to any CTF grant, applicants agree to the principles of the NF Open Science Initiative (NF-OSI), an open effort focused on finding NF treatments by sharing data and analysis results with the broader community. Please read more about our commitment to open science and data sharing here.

AWARD AMOUNT AND DURATION

Each study will be funded at **$165,000 max per year for two years**, with an optional third year of additional funding if well-justified (see information under Full Application section below). Funding amount INCLUDES indirect costs, which must not exceed 10% of the direct cost amount (eg. total $150,000 direct costs and $15,000 indirect costs).

APPLICATION PROCESS

Applications will be selected through a two-stage peer-reviewed process comprising submission of a letter of intent (LOI) followed by a full application submission upon approval of the LOI. CTF uses ProposalCentral for all stages of the grant application process.

**Letter of Intent**

Applicants must submit a LOI consisting of:

1. Project outline describing key aims/approaches of the study - Entered directly in the application form on ProposalCentral. Maximum of 4500 characters.
2. Composition of the investigative team - Entered directly in the application form on ProposalCentral.

LOI’s will be due by 5:00 pm EST on June 15, 2022. LOI’s that meet qualifications will be invited to submit a full application.

**Full application**

All invited full applications must contain:
- **Lay Abstract** - A summary of the proposed research aimed at the general public. *Entered directly in the application form on ProposalCentral. Maximum of 2500 characters.*


- **Project Description** - *To upload on ProposalCentral.*

  The Project Description (up to SIX pages excluding citations, single line spacing, Calibri size 11 font) must include background, specific aims, preliminary data (if any), experimental design, and figures where necessary. Extensive background on NF1 is not needed, only the background specifically relevant to the rationale of the strategy. There should be discussion about alternative or heterogeneous outcomes and interpretations, effects on non-tumor cells in the microenvironment, and troubleshooting. Discussion of advantages of strategy choice relative to alternatives is expected. Use of animal models must include justification describing recapitulation of the human phenotype.

  Third-year option (project extension): A plan and budget for the third year can be submitted and will be contingently approved pending the review of the first and second year milestones by CTF at the end of the second year. Applicants can also decide to submit a project extension proposal at the end of the second year.


  Please provide a list of references for the research cited.

- **Detailed Implementation Plan** - *To upload on ProposalCentral. TWO pages max.*

  Please provide specific research milestones to be met within each 6-month interval.

- **Biographical Sketch for each investigator** - *The NIH biosketch template will be provided in the application form. Applicants can also upload a biosketch generated through SciENcv.*

- **Other support**

  Please submit information on current, pending, and institutional financial support for all members of the team and any collaborators who will receive salary support from this award. All funding sources including intramural and extramural sources must be disclosed. Please indicate whether there is any overlap between any funded/pending grant and the current proposed research.
• **Budget Pages**

Please provide a detailed, itemized budget for all tasks proposed in the project plan. CTF will cover direct costs and 10% indirect costs. The two-year total must not exceed $330,000 including indirect costs. If the project proposes a third year extension, your project should not exceed $495,000 total. The third year extension will only be contingently approved, pending a review of the first and second year milestones by CTF toward the end of the second year.

*For each year, please complete a budget period on the application form on ProposalCentral.*

• **Organizational certifications and letters of support**

Appropriate certifications and letters of support are required for consideration of submitted proposals for review. In cases where ethical/regulatory approval is required to perform the work, such approvals must be provided before award activation.

• **Commitment to submit a Data Sharing Plan** - *CTF template will be available in the application form*

Applicants are required to commit to submitting a complete Data Sharing Plan (DSP) in the application submission. If the application is selected for funding, a complete DSP is required for award activation. Applicants are strongly recommended to submit the complete DSP at the time of application submission to negotiate any terms and expedite the award activation process. Please see the Award Activation section below for more information.

• **Patent Policy** - *CTF template will be available in the application form*

Applicant institutions are strongly recommended to sign the CTF Patent Policy at the time of application submission in order to speed up the process of award activation. Please see the Award Activation section below for more information.

Invited full applications will be due within 6-8 weeks of receiving notification of LOI approval. The exact due date will be indicated in the notification email from ProposalCentral.

**REVIEW PROCESS**

LOIs and full applications will be evaluated by a review panel comprised of experts from NF1 and gene therapy approaches, taking the following elements into consideration –
- Likelihood that the findings of the proposed research will have a clinical impact/implication
- Scientific merit of application and key personnel
- Feasibility of proposed study
- Alignment of budget

Applicants will be notified of the funding decision and provided peer-review comments.

**TERMS OF AWARD**

**I. Applicant Notification**
Applicants will be notified about the decision on their application within 6-8 weeks of application submission. All applicants, both funded and not funded, will be provided with a summary of the feedback from the review of their application.

**II. Award Activation**
Applicants whose proposals are selected for funding will be requested to complete and return the following documentation to CTF before their award can be activated –

- **Acceptance of Award** – An award acceptance letter will be emailed requesting information on Awardee, Institution, contact officials, and bank information for electronic transfer of payments.

- **Data Sharing** – Awardees will be required to complete a [Data Sharing Plan](#) (if not already done) and register their project as a new study on the [NF Data Portal](#). CTF believes in making data from all its funded projects freely accessible irrespective of whether the findings were positive or negative. Normally CTF allows for a 12-month embargo on the data from the end of the award after which the data will be opened to the community. For more information about the data sharing process, please visit the [Help](#) page on the NF Data Portal and the [data sharing specifications](#).

- **Patent Policy*** – Awardee institutions will be required to sign CTF’s [Patent Policy](#) before the award can be fully activated. We strongly recommend signing the [Patent Policy](#) at the time of application submission in order to speed up the process of award activation. If your institution is not able to agree to the terms of the [Patent Policy](#) as they stand, please contact us as soon as possible at grants@ctf.org. The [Patent Policy](#) is intended to ensure that any inventions or patented technologies arising from CTF-supported research are commercialized where possible. CTF anticipates recouping some revenues arising from commercialized technologies it supported, in proportion to the contribution
made by CTF's initial funding. Such funds will be used to support further initiatives at CTF.

*Special Note to Federal Employees (e.g. NIH intramural researchers)
Since the National Institutes of Health are prohibited by congressionally enacted federal law from accepting the terms of CTF's Patent Policy, the policy may be waived for federal employees, such as NIH intramural researchers, depending on the project being funded. Federal employees wishing to apply for a grant are, therefore, invited to discuss their project with CTF prior to submitting their grant proposal. Any information shared with CTF will be treated confidentially.

III. Status of Awardee
The Awardee will be considered an employee of the awardee's institution and not of CTF.

IV. Extended Leave of Absence
Should the Awardee need to take a leave of absence for more than a month for reasons such as maternity/paternity or illness, CTF must be informed of the date of departure and expected date of return.

V. Award Purpose Change or Transfer
Any fundamental change in the purpose for which the award was originally made must have prior written consent of CTF. An award may not be transferred from one institution to another without prior written authorization from CTF.

VI. Award Cancellation or Early Termination
CTF reserves the right to cancel or prematurely terminate an award if required. In such an event, the award amount will be prorated based on the number of months it was in effect. A final report of expenditures and a refund of any unspent funds must be submitted to CTF within 60 days after cancellation or termination. Failure to provide the final expenditure report by the required date will result in suspension of the award and may impact the applicant's eligibility for future funding opportunities at CTF until all materials are received.

VII. No-Cost Extension
CTF allows Awardees to request a No-Cost Extension (NCE) of the final budget period of their award for up to 1 year beyond its original expiration date. All terms and conditions specified in the original contract will apply during the extension period. Upon notification of approval by the
Program Committee, CTF will revise the project end date and provide an acknowledgment to the awardee.

VIII. Other Sources of Support
The Awardee and the sponsoring Institution are responsible for informing CTF of possible conflicts related to duplicate funding of the CTF-funded project. Failure to inform CTF of other sources of support can result in loss of CTF funding and may also jeopardize the applicant's eligibility for future funding opportunities at CTF.

IX. Periodic Reporting
Awardees are required to submit two types of reports periodically through their account on Proposal Central -

- **Progress reports (semi annual)**
  - A detailed update on the development of the CTF-funded research must be provided at 6-month intervals after activation of the award.

- **Expenditure report**
  - An expenditure update vs budget must be provided within 60 days after completion of the award.
  - All expenses must be reported in US dollars only.
  - Expenditure reports must be signed by the institution’s financial officer.
  - Any unexpended and uncommitted funds in possession of the awardee at the end of the award period must be returned to CTF within 60 days from the expiration of the award.
  - In addition to the above, interim accounting may be requested by CTF.

X. Public Notification of Awards Funded
Once an award is activated, CTF will advertise online and in CTF’s other public documentation the recipients of the award together with a lay summary of the proposed research. Please include a photograph of yourself (over 2MB resolution) that we can use in award announcements.

XI. Publicity, Publications, or Exhibits Notification of Awards Funded
The Awardee Institution must notify CTF in advance of any publications, presentations, or announcements pertaining to work done under the Award or Follow-Up Work, whether these are to professional audiences or the public media. For professional publications and presentations, once these have been accepted, Awardee Institution must submit an electronic copy of the paper, abstract, slide presentation or poster to grants@ctf.org with details of publication release or presentation (journal, meeting, time, location). CTF strongly encourages
posting of early manuscripts on preprint servers for fast acting dissemination of results. All information shall be held as confidential by CTF until time of public presentation or publication. **The support of CTF must be duly recognized everywhere, and must include the CTF grant number and the grant Digital Object Identifier (DOI) as specified in the award letter.**

For announcements to the public, the public media and/or the press, including a posting to the Internet, pertaining to this Award or any Follow-Up Work (collectively, a “Release”), Awardee Institution agrees to provide a draft of such Release to CTF at media@ctf.org at least one week before such publication of such Release so as to provide CTF the opportunity to suggest edits to the language of the Release, particularly as to CTF’s role in the Award, any Follow-Up Work, and neurofibromatosis research. Awardee Institution agrees to consider all such suggestions and include them in the Release if they are accurate. Awardee Institution shall not unreasonably decline to include any edits in a Release.

For the purposes of this Award, the term, “Follow-Up Work” shall mean any research predicated upon or directly related to the research funded by this Award.

**XII. Open Access Fee Reimbursement Policy**

CTF encourages and enables its awardees to publish in open access journals, which facilitates more rapid dissemination and broad use of their publications. To do so, we have established an annual fund of $15,000 that is available on a first-come, first-served basis to current awardees to pay the fees incurred for publishing in open access journals.

- The publication must be based on CTF-funded research.
- Requests must be submitted during the award period, or within 18 months of the award end date.
- Awardees should submit a written request to grants@ctf.org with 1) a copy of the invoice or receipt for publication fees from the journal, 2) PDF copy of the accepted publication, and 3) active URL link to the publication.

All requests will be reviewed, and if approved and if there are funds remaining, the publication fees will be duly reimbursed. If not available, authors are encouraged to explore “green open access” as a repository-based open access option within their institution.

**XIII. Follow-On Funding**

Awardees are required to keep CTF informed about any follow-on funding, collaborations, and publications (posters, papers) generated from the research funded. Such continuing communications will allow CTF to measure the impact of its research funding more easily.

Please email grants@ctf.org if you have any questions. We wish you the very best and look forward to receiving your application!